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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,512	04/06/2005	Charles Keller	007180-65	6728

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WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,512	KELLER ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11,12,14,15,17,18,20,21,23,25,26 and 28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,11,12,14,15,17,18,20,21,23,25,26 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of SEQ IFD NOS: 1, 3, 9, 13, 23, 24, 25, 33, 34, and 6 and 7 in the reply filed on September 28, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The claims 2-7, 10, 13, 16, 19, 22, 24, and 37-70 have been canceled. Claims 9, 12, 15, 18, 25 and 28 have been amended. The claim 27 has been withdrawn from consideration as being drawn to non-elected invention. The claims 1, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 23, 25, 26, 28-36 read on the elected sequences and are pending in the instant invention. Non-elected sequences are withdrawn from consideration as being drawn to non-elected invention.

Specification

2. The use of the trademark "PureGene" at page 13, "Generation" at page 13 and "SnaPshot" and "ABI Prism SnaPshot" at pages 14, 15 and 25, and "ExoSAP-IT" at page 15 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112: Lack of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 8-9, 11, 12, 14, 15, 17-18, 20, 21, 23, 25, 26 and 28-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles by performing the method steps set forth in the claims recited above, wherein said alleles for GSTM1 are GSTM1*0, GSTM1*A and GSTM1*B; said alleles for GSTM3 are GSTM3*A and GSTM3*B; said alleles for GSTP1 alleles are GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D and said alleles for GSTT1 are GSTT1*0 and GSTT1*1, it does not reasonably provide enablement for a method which detects any glutathione S-transferase allele. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a)*).

Breadth of the claims

The claims are broadly drawn to a high throughput assay for detecting glutathione S-Transferase allele or a method of assessing the potential toxicity of chemotherapy by performing PCR amplification of a portion of genomic DNA to detect GSTM1 alleles, GSTM3 alleles, GSTT1 alleles and GSTP1. The claims do not clearly define the alleles in term of their specific structure or function, e.g., in terms of a particular polymorphism or mutation that distinguishes one allele from another. The claims encompass any allelic variant of GSTM1, GSTM3, GSTT1 and GSTP1 or any other glutathione S-transferase gene.

Nature of the Invention

The claims are drawn to methods for detecting the presence of glutathione S-transferase alleles by performing amplification reactions using primers for GSTM1, GSTM3, GSTT1 and GSTp1. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

State of the Art

The specification teaches specific alleles of the GSTM1, GSTM3, GSTT1 and GSTP1 alleles (see for example pages 4, 8, 18 and Table1). Specifically, the specification teaches method for detecting GSTM1, GSTM3, GSTT1 and GSTTP1

alleles, wherein the alleles for GSTM1 are GSTM1*0, GSTM1*A and GSTM1*B, the alleles for GSTM3 are GSTM3*A and GSTM3*B, the alleles for GSTP1 are GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D, and the alleles for GSTT1 are GSTT1*0 and GSTT1*1 (see Table 1 at page 21). The specification further primers for GSTM1, GSTM3, GSTT1 And GSTP1 and teaches step of performing PCR amplification of a portion of the DNA to detect the GST polymorphisms and their use in toxicity assessment methods (see pages 3-7). However, the specification and prior art does not teach any additional GSTM1, GSTM3, GSTP1 or GSTT1 alleles as broadly encompassed by the claims.

The Predictability and unpredictability of the Art and the Degree of Experimentation Necessary:

The prior art acknowledges the unpredictability in identifying novel polymorphisms in a gene. Knowledge of the sequence of the GSTM1, GSTM3, GSTP1 and GSTT1 genes and other glutathione S transferase (GST) genes does not allow one to immediately envision specific allelic variants of these genes. The specification does not provide any information as to additional regions of GSTM1, GSTT1, GSTM3 and GSTP1 which are variable and which would be expected to contain polymorphisms which could be detected for a meaningful purpose.

The teachings of Lucentini (The scientist, December 2004, page 20) highlight the unpredictability in the art of establishing an association between a mutation/polymorphism and the occurrence of a disease or condition. As discussed by, Lucentini reproducible association studies are "few and far between". The reference

reports that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding". Lucentini teaches that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding". The reference teaches that "when they do, they usually find the link is weaker than initially estimated. The first finding is usually "spurious, or it is true, but it happens to be really exaggerated, '...there may be no way to predict which new gene association studies will be verified with multiple replication".

Without extensive information regarding the structure-function relationship between glutathione S-transferase genes and particular diseases or conditions or response to treatment, it is highly unpredictable as to what would be the identity of additional allelic variants. Thus, one cannot readily anticipate the identity of or the effect of any polymorphism as encompassed by the claims in GSTM1, GSTT1, GSTM3 and GSTP1 or other glutathione S-transferase gene. The specification does not support the broad scope of the claims. Therefore, undue experimentation is deemed necessary of one skilled in the art to practice the invention commensurate fully in scope with the claims as currently written.

Amount of Direction or Guidance Given in the Instant Specification and Working Examples:

The specification does not provide sufficient direction and guidance to practice the invention fully in scope. The specification only teaches the specific alleles of the GSTM1, GSTM3, GSTT1 and GSTP1 genes, said alleles being the following:

GSTM1*0, GSTM1*A, GSTM1*B, GSTM3*A, GSTM3*B, GSTP1*A, GSTP1*B, GSTP1*C, GSTP1*D, GSTT1*0 and GSTT1*1 (see Table 1 at page 21). The specification does not provide any specific guidance as to how one is to predictably identify additional GSTM1, GSTM3, GSTP1 and GSTT1 alleles or other glutathione S-transferase alleles. Further, the specification does not provide any guidance as to whether these undisclosed alleles of GSTM1, GSTM3, GSTP1 and GSTT1 alleles or other glutathione S-transferase alleles are useful for determining a disease condition or assessing toxicity of chemotherapy.

To identify additional alleles of GSTM1, GSTM3, GSTP1 and GSTP1 genes which could be used for a meaningful purpose would require extensive experimentation. For example, such experimentation may involve sequencing the GSTM1, GSTM3, GSTP1 and GSTT1 genes of individuals affected with a particular disease, such as cancer, sequencing the GSTM1, GSTM3, GSTP1 and GSTT1 genes of normal/ control individuals, comparing the sequences of these two groups, and then identifying variations which are present only in the affected group and not in the control group, such random, trial by error experimentation is considered be undue.

While methods for identifying polymorphisms are known in the art, such method provides only the general guidelines that allow researches to randomly search for polymorphisms that may be liked to a disease or a response to therapy. The results of performing such methodology are highly unpredictable. The specification has not provided only an invitation to experiment. The specification however does not provide a predictable means for identifying additional alleles of GSTM1, GSTM3, GSTT1 and

GSTP1 genes. The specification does not provide any working examples which depict additional alleles of GSTM1, GSTM3, GSTT1 and GSTP1 genes or other glutathione S-transferase alleles.

Conclusion

Case law has established that "[t]o be enabling the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'". *In re Wright* 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance need to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genetech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches a total of 11 alleles of the GSTM1, GSTM3, GSTT1 and GSTP1 genes. The specification does not teach a representative number of additional alleles of thee gene or any other glutathione S-transferase genes in order to enable methods which detect any GSTM1, GSTM3, GSTT1 and GSTP1 allele, wherein the alleles are not defined in terms of their structure or function.

In view of the unpredictability in the art, extensive experimentation would be required to identify additional allelic variants of the GSTM1, GSTM3, GSTT1 and GSTP1 gene. Given the lack of disclosure in the specification and in the prior art and the unpredictability in the art and the level of skill in the art, it would require extensive and undue experimentation for one skilled in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 112: Second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims 1, 8-9, 11, 12, 14, 15, 17, 18, 20, 21, 23, 25, 26 and 28-36 are indefinite at the recitation of "detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles" because it is unclear as to what is intended to be encompassed by these alleles. While the claims refer to GSTM1, GSTM3, GSTT1 and GSTP1 alleles, the claims do not set forth the structure or sequence or any other identifying characteristics of these alleles. Further theses phrases lack proper antecedent basis as none of the previous steps recite individuals alleles of GSTM1, GSTM3, GSTT1 and GSTP1. Rather the claims recite glutathione S-transferase alleles. Clarification is required.

(b) The claims 28, 29, 31 lacks proper antecedent basis for "the gene dosage" because neither the claim 20 nor the claim 1 recite any "gene dosage". It is suggested amending the claims such that the claim language agrees.

Claim Rejections - 35 USC § 102(b)

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Jourenkova-Mironova et al (Int. J. Cancer, vol. 81, pages 44-48, 1999). Regarding claim 1, Jourenkova-Mironova et al teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (abstract and section entitled "Materials and Methods", beginning at col. 2 of page 44 to col. 1 on page 46). Therefore, Jourenkova-Mironova et al meet the limitations of claim 1.

9. Claims 1, 8 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ko et al (Pharmacogenetics, vol. 10, pages 271-274, 2000). Regarding claim 1, Ko et al teach a method for detecting GST alleles present in a patient comprising the steps of:

obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (see page 271, col. 2 to page 273, col. 1).

Regarding claim 8, Ko et al teach wherein the step of performing PCR amplification of a portion of the DNA to detect GSTM1 alleles comprising fluorescent, allele, specific PCR using GSTM1-specific primer sequences (page 272 and Table 1).

Regarding claim 17, Ko et al teach wherein the step of performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms comprises performing fluorescent, allele-specific PCR using GSTP1 specific primer sequences (page 272 and Table 1). Therefore, Ko et al meets the limitations of the claims recited above.

Claim Rejections - 35 USC § 102(a)

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Lan et al (Pharmacogenetics, vol. 22, pages 655-661, November 11, 2001). Regarding claim 1, Lan et al teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (see section entitled "Materials and Method", page 656-657).

Regarding claim 14, Lan et al teach wherein the step of performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles comprises performing PCR using GSTM3 and GSTT! Specific primer sequences (see page 656, col. 2). Therefoe, Lan et al meets the limitations of the claims recited above.

12. Claims 1 and 14 are rejected under 35 U.S.C. 102(a) as being as being anticipated by Buch et al (Carcinogenesis, vol. 23, no. 5, pages 803-807, 2002). Regarding claim 1, Buch teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to

detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (see section entitled "Materials and Methods", page 804, col. 1).

Regarding claim 14, Buch teach wherein the step of performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles comprises performing PCR using GSTM3 and GSTT1 specific primer sequences (see page 804 section entitled "Materials and Method, col. 1). Therefore, Buch et al meet the limitations of the claims recited above.

13. Claims 9, 14, 15, 20, 21 and 23 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jourenkova-Mironova et al as previously applied above in view of Waschuetza, S (WO 0136670, effective filing date June 2001) and further in view of Buck et al (Biotechniques, vol. 27, pages 528-536, September 1999). Regarding claim 9, 14, 15 and 36, Jourenkova-Mironova et al teaches a method for detecting GST alleles present in a patient comprising the steps as previously described above wherein GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles are detected.

Jourenkova-Mironova et al do not teach wherein individual GSTM1 is detected using GSTM1-specific primers comprising the sequence of SEQ ID NO: 1 or SEQ ID NO: 3. or the GSTM3 and GSTT1 specific primers comprising the sequence of SEQ ID NO: 24 and 25.

Waschuetza teaches a method for detecting glutathione S-transferase allele by performing PCR (see also page 5 of translated pages which teaches PCR and primers used in amplification of GST alleles), wherein one of the primers used in the amplification reaction is substantially identical to the sequence of SEQ ID NO: 3 (see Abstract and sequence of GSTM1-A at page 14, line 35 of original document and page 5 of translated document):

GSTM1 A (Waschuetza) TTGGGAAGGCGTCCAAGCGC

SEQ ID NO: 3 TTGGGAAGGCGTCCAAGCA

(See also GSTM1-B at page 15, line 1):

GSTM1-B (Waschuetza) TTGGGAAGGCGTCCAAGCAG

SEQ ID NO: 3 TTGGGAAGGCGTCCAAGCA

With regards to claims 14 and 15, Waschuetza teaches a method for detecting glutathione S-transferase allele by performing PCR, wherein one of the primers used in amplification reaction is substantially identical to the sequence of SEQ ID NO: 24 and SEQ ID NO: 25 (see page 11, line 32 of orginal document and page 5 of translated document):

GSTT1 (Waschuetza) TTCCTTACTGGTCCTCACATCTC

SEQ ID NO: 24 & 25 TTCCTTACTGGTCCTCACATCTC

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of

identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Waschuetza and which are 95% derived from sequences expressly suggested by the prior art and known in the prior art as disclosed by Waschuetza as useful for primers specific for GSTM1, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes “Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).”

With regard to the issue of reasonable expectation of success in using such

equivalents, Buck et al expressly provides a general teaching of evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95-control primers functioned, which represent 1/3 of all possible primers in the target region.

This clearly shows that every primer would have a reasonable expectation of success.

With regards to claims 20, 21 and 23, Waschuetza teaches the use of gel electrophoresis and capillary gel electrophoresis to analyze amplified DNA products (page 7 of the translated pages).

With regards to claim 36, Waschuetza teaches that the method is used to identify polymorphisms of decontamination enzymes in a simple and safe and standardized way

(page 4, 5th paragraph of translated pages). Waschuetza also teaches wherein the method can used in some cases to determine appropriate therapy for a patient impacted with chemical or drug toxicity (see page 2, last two sentences of second paragraph of translated pages and page 3, six paragraph of page 3 of the translated pages). Waschuetza et al teaches a link between GST and toxicity (page 1 and 2

Therefore, it would have been obvious to one of ordinary skill in the art to compare polymorphic alleles of GST to evaluate potential toxicity as taught by Waschuetza. Using the known technique of performing PCR to compare GST polymorphic alleles and its relationship to drug toxicity or to determine suitable therapy for a patient would have been obvious to one of ordinary skill in the in the absence of secondary consideration.

14. Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jourenkova-Mironova et al as previously applied above in view of Klagsbrun et al (WO 9919488, April 1999) and further in view of Buck et al (Biotechniques, vol. 27, pages 528-536, September 1999). Regarding claims 11-12, Jourenkova-Mironova et al teaches a method for detecting GST alleles present in a patient comprising the steps as previously described above wherein GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles are detected.

Jourenkova-Mironova et al do not teach wherein individual GSTM1 is detected using GSTM1-specific primer comprising the sequence of SEQ ID NO: 6 or SEQ ID NO: 7.

Klagsbrun et al teach a method for detecting a target nucleic acid, wherein said target is a beta-actin cDNA by performing PCR. Klagsbrun teachs a complementary sequence that is substantially identical to the sequence of SEQ ID NO: 6 (see page 43, line 28:)

SEQ ID NO: 29, Klagsbrun) 19 CCTCCCTGGAGAAGAG 4

SEQ ID NO: 6 1 CCTCCCTGGAGAAGAG 16

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Klagbrun et al and which is derived from sequences expressly suggested by the prior art and known in the prior art as disclosed by Waschuetza as useful for primers specific for a beta-actin cDNA, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes

"Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck et al expressly provides a general teaching of evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used

by 39 different laboratories. It is particularly striking that all 95-control primers functioned, which represent 1/3 of all possible primers in the target region.

This clearly shows that every primer would have a reasonable expectation of success.

15. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jourenkova-Mironova as previously applied above in view of Sprenger et al (citation made of record on IDS) and further in view of Buck et al (citation recited above). Regarding claims 28-30, Jourenkova-Minovona et al teach a method for detecting GSTM1, GSTM3, GSTT1 and GSTP1 using PCR amplification steps.

The reference does not teach performing a long range PCR assay to determine the gene dosage of GSTT1 using GSTT1*0 specific primer sequences comprise the sequence of SEQ Id NO: 33 and 34.

Sprenger et al teaches a method of determining a gene dosage of GSTT1 by performing long range PCR and wherein the PCR reaction comprises the use of GSTT1*0 specific primer sequences (page 2, 4, and Table 3 page 19). Sprenger et al further teach a sequence that is substantially identical to the sequence of SEQ ID NO: 33 (see page 11, SEQ ID NO: 2 at nucleotides 4978 to 4999) and a sequence that is substantially identical to SEQ ID NO: 34 (see page 11, claim 3 at line 2).

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding

structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Sprenger et al and which is derived from sequences expressly suggested by the prior art and known in the prior art as disclosed by Sprenger as useful for primers specific for GSTT1*0, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes “Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).”

With regard to the issue of reasonable expectation of success in using such equivalents, Buck et al expressly provides a general teaching of evidence of the

equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95-control primers functioned, which represent 1/3 of all possible primers in the target region.

This clearly shows that every primer would have a reasonable expectation of success.

Conclusion

16. No claims are allowed. However, some of the claims have not been rejected under prior art. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone

number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Patent Examiner
Art Unit 1637